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SYSTEMATIC REVIEW

Herbal interventions for chronic asthma in adults and children: a systematic review and meta-analysis

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Abstract

Aims: To assess the efficacy of herb and plant extracts in the management of asthma.

Method: Systematic review and meta-analysis. Multiple database searches identified randomised placebo controlled trials of herbal interventions reporting at least one primary outcome measure. Where possible data were combined for meta-analysis. Primary outcome measures were lung function, exacerbations and reduction in corticosteroid use. Secondary outcome measures were symptoms and symptom scores, use of reliever medications, changes in rates of consultation and adverse effects.

Results: Twenty-six studies reporting on 20 herbal preparations were included. Two of six studies reporting change in FEV_1 were positive. Little data was available on frequency of exacerbations. For primary outcomes single studies of Boswellia, Mai-Men-Dong-Tang, Pycnogenol, Jia-Wei-Si-Jun-Zi-Tang and Tylophora indica showed potential to improve lung function, and a study of 1.8-Cineol (eucalyptol) showed reduced daily oral steroid dosage.

Conclusions: Improvements in symptoms were not strongly supported by objective changes. Most trials were of small sample size, short duration, and poor methodology. Further adequately powered trials are needed to assess these compounds. Such trials should conform to CONSORT guidance, report standardised spirometry, and use validated symptom and severity scores. No recommendations for herbal treatment of asthma can be made from the current evidence.

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The full version of this paper, with online Appendix 1, is available online at www.thepcrj.org

Introduction

The use of complementary or alternative medicine (CAM) is widespread in asthma. Only 41% of UK asthma sufferers have not used CAM and of those two-thirds would consider using it in the future.[1] Herbal remedies are a consistently popular form of CAM in asthma[1-3] and proprietary asthma drugs are derived from herbal remedies – for example, ephedrine was developed from the traditional Chinese remedy 'ma huang', and tea leaves are the herbal origin of theophylline.[4] Caffeine, related to theophylline, has been used for centuries to treat asthma and a Cochrane review found that it improved lung function for up to four hours after ingestion.[5]

Complementary interventions are often used along with conventional medicines for asthma,[6,7] with 81% of herbal therapy users also using conventional medicines in one study,[8] often because CAM is perceived to be safe. However, there are risks such as contamination, natural toxicity and drug interactions.[9] The latter is of concern since users are less likely to consult their general practitioner (GP) because of an adverse reaction to a herbal remedy than for a conventional over-the-counter medicine.[10]

A previous systematic review of herbal treatment for asthma in 2000 found 17 randomised controlled trials (RCTs) assessing

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traditional Chinese herbs, Indian remedies, one Japanese herbal preparation, dried ivy-leaf extract, and marijuana.[11] Methodological quality of the trials was poor and it was concluded that herbal products are of uncertain value in the treatment of asthma. Since herbal products remain popular for asthma, an update of the current evidence was needed. Therefore we have conducted a Cochrane systematic review[12] and the findings are summarised in this paper.

Methods

Searching

We searched for trials (search strategy, see Table 1) from the following sources: The Cochrane Airways Group Specialised Register; Cochrane Complementary Medicine Field Specialised Register; The Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (1966 to present); OLDMEDLINE (1950 to 1965); EMBASE (1980 to present); AMED (1985 to present); HerbMed; Chinese Biomedical Database (1975 to 2006); China National Knowledge Infrastructure (1979 to 2006); VIP database (1979 to 2006); and the UK National Research Register and Clinicaltrials.gov. Reference lists of review articles and studies were checked for additional trials. Authors of studies were contacted for further information if necessary, and we had contact with the Cochrane Complementary Medicine Field, Chinese Cochrane Centre and Asthma UK.

Table 1. Search strategy used in the CENTRAL database on the Cochrane Library, and adapted for other database searches.

#1 ASTHMA (MeSH)
#2 asthma*
#3 wheez*
#4 bronchospas*
#5 bronch* NEAR spas*
#6 bronch* NEAR constrict*
#7 bronchoconstrict*
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MEDICINE, HERBAL (MeSH)
#10 PLANT PREPARATIONS (MeSH)
#11 PLANTS, MEDICINAL (MeSH)
#12 PHYTOTHERAPY (MeSH)
#13 MEDICINE, TRADITIONAL (MeSH)
#14 herb*
#15 plant*
#16 phyto*
#17 botanic*
#18 tradition* NEAR medicine*
#19 chinese* NEAR medicine*
#20 ayurvedic*
#21 kampo*
#22 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 #8 AND #22

Inclusion criteria

We searched for randomised or quasi-randomised controlled trials recruiting adults and/or children over five years old with asthma diagnosed on the basis of symptoms and lung function assessment. Herbal medicine was defined as the use of plants or plant extracts to treat asthma. Preparations could be a single herb or a mixture derived from the leaves, stems, buds, roots, fruit or bark[6] and administered by any means except smoking. Single chemical extracts or synthetic plant-based chemicals were not included. The intervention could be given either as a sole agent or in addition to usual treatment, but a placebo control arm was necessary. We did not include trials comparing one herbal intervention with another, or with any other complementary treatment.

Primary and secondary outcome measures

Trials had to report at least one of the following primary outcome measures: changes in lung function; rates of exacerbations; or use of corticosteroids. We also extracted secondary outcome measures: changes in symptoms or symptom scores; use of reliever medications; rates of consultation; and withdrawal or drop-out rates. Adverse effects were also noted.

Study selection, data extraction and quality assessment

Results of the literature search were screened by two reviewers (CEC & EA). Potentially relevant trials were identified from title, abstract and keywords and we retrieved the full texts to assess studies for inclusion, obtaining translations where necessary. Data were extracted independently by two authors (CEC & EA) using a standard data extraction form and disagreement was resolved by discussion and/or the third author (TJL). Trialists were contacted for further information and unpublished data if necessary, and data were estimated from graphs presented in two RCTs.[13,14] Data were entered into Review Manager software[15] by one author (EA) and checked for accuracy by another (TJL).

Risk of bias was assessed in terms of generation of the randomisation sequence, allocation concealment, and blinding as adequate, uncertain or inadequate using Cochrane criteria.[16]

Data analysis

Separate analyses were conducted for each type of herbal preparation against placebo. Treatment effects were calculated as the relative risk (RR) with 95% confidence intervals (95%CI) for dichotomous data. For continuous data, we calculated mean difference (MD) with 95% confidence intervals for outcomes reported in the same scale, and a standardised mean difference (SMD) with 95% confidence intervals for outcomes reported in different scales. Analysis employed a fixed-effects model in comparing sub-groups of

single studies and a random-effects model in pooling data across different studies.

Data from the first phase of cross-over trials were extracted and analysed with parallel-group trials. If these data were not available, cross-over trials were analysed using generic inverse variance (GIV). Subgroup and sensitivity analyses were planned but insufficient data were extracted to carry any out.

Results

We retrieved a total of 2,645 references electronically, a further 111 studies by searching Chinese databases in China (TW), and one by correspondence (from Asthma UK). After reviewing full texts, 226 studies were excluded (Figure 1) and 26 studies (28 experimental comparisons) met the entry criteria, randomising 1,879 participants.

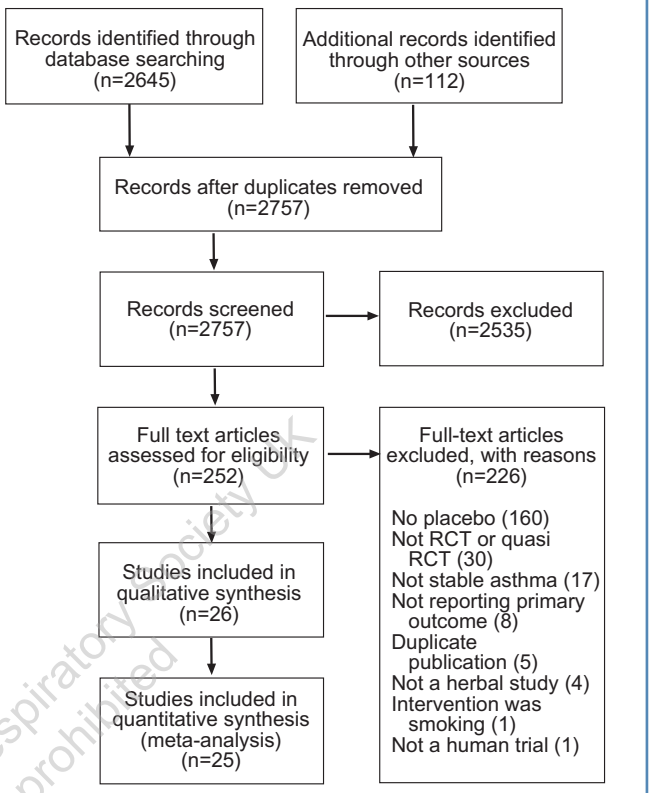
Description of studies

One study used a quasi randomised design[13] and the design of one other[17] was unclear as the allocation method was not stated (clarification was sought from the authors but not received). The remainder were RCTs using either parallel groups[14,18-30] or a crossover design.[31-40] All were double blinded except one single blinded study where the colours of study and placebo medicine sachets differed.[26] Sample sizes ranged from eight[32] to 334,[13] six studies recruited children[13,14,19,23,24,35] – although one of these reported subjects up to age 55[24] (clarification was sought but not received) – and one a mixed age group of 14-20 yrs.[21] Age was not stated in five studies,[17,25,27,37,38] and the remainder recruited adults. Inclusion criteria required demonstration of reversibility in five studies,[18,24,34,35,38] meeting existing diagnostic criteria for asthma in ten studies,[13,14,18,19,23,27,29,30,33,40] or a clinical diagnosis or history of asthma in ten.[17,20-22,25,28,31,32,36,37] Inclusion criteria were not stated in one study.[39] Subjects were recruited as in-patients in one study,[22] out-patients in ten,[13,14,18-21,30,33-35] from both sources in three studies,[17,36,37] or were not stated for the remainder. Included studies are summarised in online Appendix 1 (see www.thepcrj.org).

Interventions and outcome measures

A total of 20 different study drugs were compared with placebo (Table 2). Mean duration of treatment was 8.4 weeks, ranging from three days[32] to 12 months.[29] Primary and secondary outcome measures were reported as follows: forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) in 14 studies[17-19,21,24,27-30,32-34,39,40] or changes from baseline in four;[22,26,35,38] peak expiratory flow rate (PEFR) in eight[18,19,21,22,24,30,31,39] or changes in PEFR in five;[13,14,22,28,38] vital capacity (VC) in three;[28,35,38] FEF25-75 in one[34] and maximum breathing capacity (MBC) in one.[38] Three studies recorded exacerbation rates,[18,22,39] six changes in medication use,[14,19,28,30,31,37] and 14 recorded symptom scores.[13,14,21,24-26,28,30,33,36-40] Five trials reported subjective assessments.[13,14,20,22,27]

Figure 1. PRISMA flowchart of review.



Methodological quality

Reporting quality of studies was generally poor and methodology could only be assessed in a minority. Randomisation was adequately described in six trials (23%) and allocation concealment in six (23%). Blinding was adequately described in 22 studies (85%; Figure 2); one of these used an emetic (Ipecacuanha) to mask the side effect of the intervention (Tylophora).[22] Only seven studies (27%) reported withdrawals[13,19,23,24,28,34,35] and only one study gave adequate descriptions of all three domains.[24]

Outcome measures and data synthesis

Twenty-five studies (27 experimental groups) contributed data to the analysis. One study of Evening Primrose Oil did not contribute numerical data, but reported no significant difference for the asthma sub-group which we confirmed in correspondence with the author.[23] Since studies reported individually-defined measures of changes in lung function, meta-analysis was only possible within subgroups of single studies of Boswelia[18] and Mai-Men-Don Tang,[24] and between studies of Tylophora indica.[21,25,36,37]

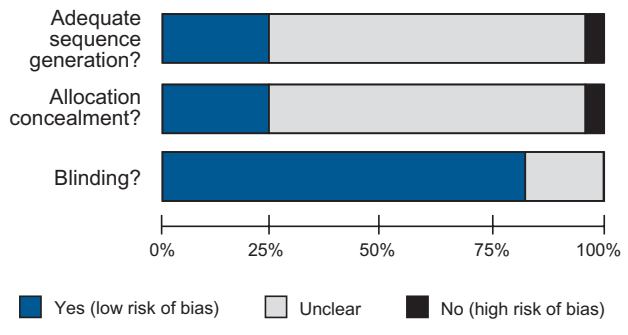
Primary outcomes

The majority of studies reported no significant differences in measures of lung function or corticosteroid dosage. Individual studies showed significant differences in measures of FEV_1 for

Table 2. Compounds included in the review.

Type	Name	Ingredients or origin
Traditional Chinese Medicines	Mai-Men-Dong-Tang	*Ophiopogon, American ginseng, Pinellia, Licorice, Lantern tridax*
	Liu-Wei-Di-Huang-Wan	*Rehmannia root, Alisma rhizome, Dioscorea rhizome, Poria, Hoelen, Moutan root bark, Shanzhu yu*
	Shen-Ling-Bia-Shu-San	*Ginsheng root, Rhizomeatractylodes, Ovata, Licorice root, Dioscorea rhizome, Lablab seed, Coix seed, Lolus fruit, Tangerine peel, Amomn seed, Platycodon*
	Jai-Wei-Si-Jun-Zi-Tang	*Ginsheng root, Atractylodes ovata rhizome, Poria Hoelen, Licoroce root, Ginger root, Jujube, Ophiopegon tuber, Schisandra fruit, Psoralea seed*
	Ding Chuan Tang*	Decoction of 9 herbs: *Ginkgo biloba, Ephedra sinica, Tussilago farfara,Morus alba, Pinellia ternata, Perilla frutescens,Prunus armeniaca, Scutellaria baricalensis, Glycyrrhizauralensis.*
Indian	Tylophora indica	
	Devadaru compound	Decoction of 6 plants: Devadaru (*Cedrus deodara*), Vacha (*Acorus calamus*), Kantakari (*Sdanum xanthocarpum*), Sunthi (*Zibgiber officinale*), Katpal (*Myrica ndgi*) and pushkarmool (*Inula recemosa*)
	Pulmoflex	Traditional Ayurvedic medicine containing standardised extracts of *Adhatoda vasica, Solanum xanthocarpum, Glycyrrhiza glabra, Sida cordifolia, Albezia lebbeck, Alpinia galanga, Suassurea lappa, Ocimum sanctum, Piper longum, Zingiber officinale* and *Hedychium spicatum*
	Herbal compound *DCBT4567-Astha-15*	Extracts of: *Woodfordia fruiticosa, Solanum xanthocarpum, Adathoda vasika, Acacia arabica, Ellateria cardamomum,Piper nigrum, Achyranthus aspera, Zingiber officinalis, Hollarhena antidysenterica, Circuma longa, Syzygium aromaticum, Calotropis procera, Enicostemma littorale, Piper longum*
Japanese	TJ-96 "Saiboku-to" or *"Chai-pu-tang"*	A mixture of 10 herbs, including magnolol, an extract of *Magnolia officinalis*. Other ingredients not described.
Other	Ivy leaf extract	
	Gammalinolenic acid-containing oil (Borage oil)	Borage
	Ginkgolides or Ginkgo containing compounds	
	1.8-cineol (eucalyptol)	Major constituent of eucalyptus oil.
	Butterbur	*Petasites hybridus*
	Menthol vapour	Peppermint oil
	Pycnogenol	Extract of French maritime pine bark, *Pinus maritime*
	Boswellic acids	Frankincense plant (*Boswellia carterii*)
	Efamol	Evening primrose seed oil (*Oenothera biennis*)
	Ginger	

Figure 2. Risk of bias graph; summary of judgments of each risk of bias item assessed.



Mai-Men-Dong-Tang,[24] Boswellia,[22] and TJ-96-Saiboku-to,[40] in PEFR for Boswellia[22] and Pycnogenol (French Maritime pine bark extract) in children,[14] and in FVC for Boswellia[22] (see online Appendix 1 at www.pcrj.org).

Five studies of Tylophora indica were included.[21,25,36-38] One did not report any confidence intervals[38] and there was significant heterogeneity between the studies which restricted pooling of data. One study reported higher rates of >15% increase of FEV_1 and >20% increase of PEFR compared with placebo[25] whereas another did not.[21] The reported improvement in PEFR after six days of treatment remained at 12-week follow-up.[25]

One study of 1.8-cineol (eucalyptol) reported a significant reduction in oral steroid dose (2.84mg; 95%CI 1.00 to 4.68)

Figure 3. Tylophora indica vs. placebo, symptom score improvement >50% (week 1).

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Gupta 1979	18	71	11	64	39.8%	1.48 (0.76, 2.88)
Mathew 1974	34	59	15	64	60.2%	2.46 (1.50, 4.03)
Total (95% CI)		130		128	100.0%	2.01 (1.23, 3.28)
Total events	52		26			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.45$; df = 1 (p = 0.23); p = 31%
Test for overall effect: Z = 2.78 (p = 0.006)

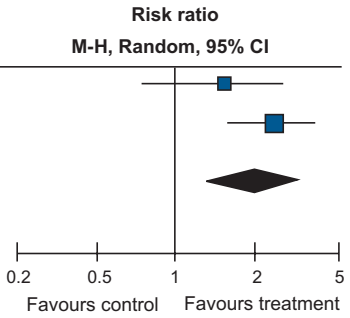
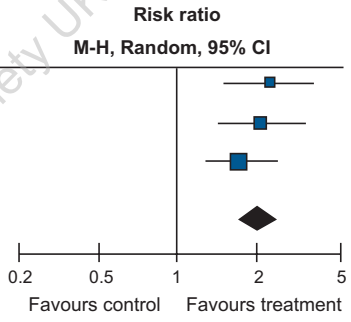


Figure 4. Tylophora indica vs. placebo, total clinical improvement >50% (week 1).

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Mathew 1974	34	59	15	64	24.0%	2.46 (1.50, 4.03)
Shivpuri 1969	33	53	16	57	27.0%	2.22 (1.39, 3.53)
Shivpuri 1972	58	103	29	92	49.0%	1.79 (1.26, 2.52)
Total (95% CI)		215		213	100.0%	2.05 (1.61, 2.61)
Total events	125		60			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.24$; df = 2 (p = 0.54); p = 0%
Test for overall effect: Z = 5.79 (p < 0.00001)



and a significant difference in the number of patients tolerating a 5 mg reduction in steroids (RR=3.00 95%CI 1.23 to 7.34).[30]

Secondary outcomes

Symptoms

Improvements in symptom or symptom scores against placebo were demonstrated in studies of 1.8-cineol (eucalyptol) (dyspnoea score, patients', and physicans' global assessments of efficacy),[30] Ginger (dyspnoea, wheeze and chest tightness),[27] Pulmoflex (patients experiencing a deterioration),[20] Pycnogenol in children (symptom score)[14] but not in adults,[33] and Liu-Wei-Di-Huang-Wan and Shen-Ling-Bai-Shu-San (symptom scores).[13]

Data pooled from two studies of Tylophora indica (n=258) showed that after six days of treatment symptom scores were more often improved by at least 50% at one week (RR 2.01; 95%CI 1.23 to 3.28, Figure 3).[21,25] This persisted at 12 weeks for one study (RR 2.17; 95%CI 1.00 to 4.69, n=123),[25] but the other study found no significant difference two weeks after treatment.[21] There were higher rates of >50% improvement in physical sign scores for Tylophora indica compared with placebo after one week (RR 1.87; 95%CI 1.18 to 2.96) and 12 weeks (RR 2.58; 95%CI 1.22 to 5.43, n=123) reported by one study,[25] and pooled results from three studies showed a higher rate for total clinical improvement >50% after one week (RR 2.05; 95%CI 1.61 to 2.61, p<0.001, n=428, Figure 4) but this was no longer significant after 12 weeks (RR = 1.58; 95%CI 0.60 to 4.16, p=0.35, n=381).[25,36,37]

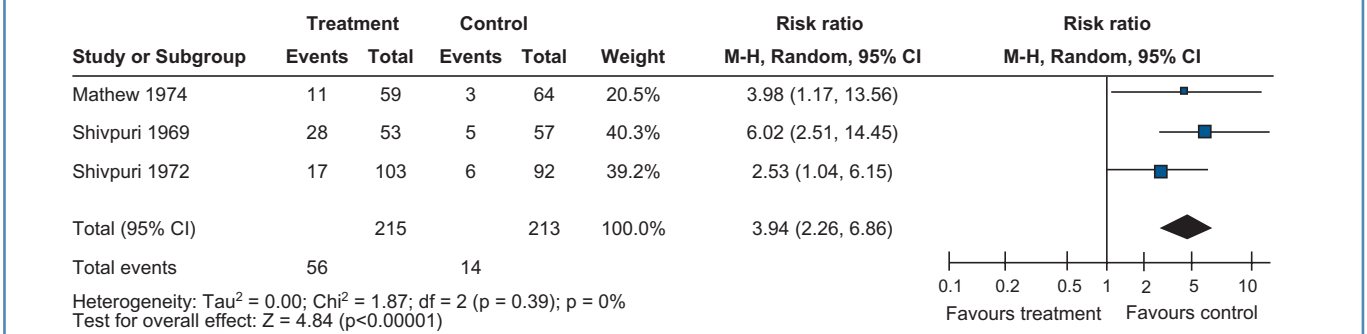
Medication use

Compared with placebo, use of albuterol was significantly reduced in the study of Pycnogenol in children (mean 0.22 puffs/24hrs vs 2.32, MD -2.10; 95%CI -2.53 to -1.67, p<0.001),[14] and use of reliever inhalers was significantly reduced in the study of Menthol vapour (mean 2.1 puffs/week vs 4.4, MD -2.30; 95%CI -3.13 to -1.47, p<0.001). Drug consumption scores were more frequently reduced by >50% after one week and 12 weeks in one study of tylophora indica (week 1: RR 2.60, 95%CI 1.60 to 2.24, p<0.001 and week 12: RR 2.29, 95%CI 1.13 to 4.66, p=0.02).[25]

Adverse effects

Pooled data for three studies of Tylophora indica showed that significantly more study than control subjects reported side effects after one week (RR 3.94; 95%CI 2.26 to 6.86, p<0.001, n=428, Figure 5)[25,36,37] they reported loss of salt taste, sore mouth, abdominal pain, nausea and vomiting. A further study of tylophora not included in the analysis reported similar side effects.[21] Gastrointestinal side effects were also reported with Boswelia (nausea, epigastric pain and hyperacidity),[22] 1.8-cineol (eucalyptol) (heartburn and gastritis),[30] Traditional Chinese Medicine (TCM) (abdominal

Figure 5. Tylophora indica vs. placebo, number of patients experiencing side effects (week 1).



pain and unpleasant taste),[13] and Pycnogenol (gastrointestinal disturbance)[33] in adults. There were two withdrawals in the study of menthol vapour due to upper airway discomfort.[28]

Discussion

Summary of main findings

Herbal preparations are frequently used in the management of asthma. We identified 26 trials of 20 herbal preparations meeting our entry criteria. The majority of studies reported no significant differences in measures of lung function or corticosteroid dosage and no meta-analysis of data for primary outcomes was possible. Individual studies reported improvements in the primary outcome measures of FEV_1 for Mai-Men-Dong-Tang,[24] Boswellia,[22] TJ-96-Saiboku-to,[40] and Tylophora indica;[25] improvements in PEFR for Boswellia,[22] Pycnogenol (French Maritime pine bark extract) in children,[14] and Tylophora indica;[25] and improvement in FVC for Boswellia.[22]

Strengths and limitations of this study

There were wide variations in study design, the interventions studied, and the outcome measures presented. For example, FEV_1 was reported in five different ways across 17 studies. In addition there was marked heterogeneity between study results, therefore meta-analysis of data was only possible between combinations of four studies of tylophora,[21,25,36,37] and in combining sub-groups within one study of Boswelia[18] and one study of Mai-Men-Dong-Tang.[24] The reporting quality of the studies was poor and only one gave adequate descriptions of randomisation, blinding and withdrawals;[24] therefore sensitivity analysis by study quality and assessment of publication bias was not feasible. The inconsistencies and poor quality of reporting in these trials leaves the validity of these results open to question, and positive outcomes for many of the studies should be interpreted in this context.

There were improvements reported in subjective asthma symptoms for many compounds but the way in which these symptoms were reported also differed vastly – for example Pulmoflex[20] showed improvement in "patients experiencing deterioration" while Ginger[27] showed improvement in "patients experiencing chest tightness". Values for Chinese herbs Liu-Wei-Di-Huang-Wan, Shen-Ling-Bia-Shu-San, and Jai-Wei-Si-Jun-Zi-Tang[13] had to be estimated from graphs, and there were issues with the adequacy of blinding in these trials.

Potential confounding variables were generally poorly described. For example, of the 20 studies recruiting adults, four explicitly excluded smokers,[18,26,28,40] one reported smoking rate,[17] but 15 did not describe smoking status at all. This uncertainty limits the applicability of findings to other populations.

Comparison with existing literature

There is a considerable literature for studies of TCM but methodological limitations meant that many trials identified from our searches did not meet our entry criteria for the review. Few of the trials used a placebo control or undertook allocation concealment. A large number were described in study reports as having a randomised design, but when contacted 95% of authors did not understand the concept of randomisation.[12] Chinese medicinal herbs are widely accepted as a treatment for asthma in China, but most of the constituents of pharmacologically-prepared drugs used in trials were not clearly specified. There is variation in the formulations of TCM preparations and, although the Chinese Government does specify acceptable limits of variation, this may contribute to differing study results.

Implications for clinical practice

Five studies of Tylophora indica were included; meta-analysis of two showed improvement in symptoms scores (>50%) after one week[21,25] and of three showed clinical improvement (defined as at least 50% reduction in frequency of attacks and only moderate symptoms) after one week but not 12 weeks.[25,36,37] One study showed a greater than 20% improvement in PEFR and greater than 15% improvement of FEV_1 after one week of treatment and this remained significant at 12 weeks follow-up.[25] Tylophora has been postulated to have an effect persisting for weeks after the six days of treatment used in these studies, but no other

objective measure of improvement was seen after 12 weeks. In fact, it may not be suitable for prolonged use since gastrointestinal side effects, severe enough to justify use of an emetic as placebo for one study,[25] were prominent in four studies.[21,25,36,37]

A significant rise in FEV_1 (400ml) was reported with Boswelia in one study[22] and in the other a significant improvement in FEV_1 % predicted was found.[18] The small sample subgroups drawn from this study may bias the pooled effect, and the changes translated into only small changes in actual FEV_1 (estimated 210mL) and PEFR (44.5 L/min)[22] in clinical terms. A significant improvement in PEFR was also reported for Pycnogenol in children[14] but again this represented a modest absolute change of PEFR (estimated 70L/min).

One study assessing the effect of eucalyptol as an oral steroid-sparing agent reported a mean reduction of 3 mg in daily dose associated with a significant decrease in symptoms.[30] This is of potential clinical benefit but longer follow-up would help to establish whether this effect can be sustained beyond the 12-week study period. Oral steroid dosages at entry ranged from 5 to 24 mg prednisolone daily, implying that subjects were a selected group of severe asthmatics. Therefore, although it is registered in Germany as a medicinal product for the treatment of asthma,[30] further studies of eucalyptol in mild to moderate asthma, and assessment of any effects on inhaled corticosteroid dosage, are needed before it can be concluded to have a useful anti-inflammatory effect.

It is commonly perceived that herbal treatments for asthma are safe; however, their use has been associated with increased hospital admissions.[41] In this review only 16 studies considered adverse effects but nine of these did report their presence. Symptoms were predominantly gastrointestinal and for some studies dropout rates were significant.[24,37]

Implications for future research

There is some evidence for benefit from individual studies of Tylophora but further assessments longer than six days in duration are needed. It is likely that further work to differentiate the active ingredient(s) from the causes of the substantial side effects will also be required before longer studies can be performed. The potential steroid-sparing effect of eucalyptol is also interesting, but needs verification in a more representative study of mild to moderate asthmatics.

Extrapolating the findings of the studies in this review to a more general population is hampered by the poor reporting quality of the original studies. Sixteen trials were reported after the publication of the CONSORT statement in 1996,[42] but only four of these[19,24,26,30] report both the method of randomisation and blinding. It is therefore questionable whether the positive findings in this review could be used to inform a decision to use any of the treatments studied. The CONSORT statement has been extended for the reporting of RCTs in herbal interventions[43] and future studies should take account of its recommendations. It is also important that any self-prepared herbal formulation that is assessed in a clinical trial is described in detail, in terms of the type of herb used, and the methods used in its preparation. Therefore, priorities for future trials include better reporting of methodology, more open disclosure of outcome data, and clear reporting of baseline characteristics. Reporting of standardised recognised measures of lung function and validated rather than bespoke symptom scores would facilitate comparison and inform decisions when considering the use of herbal preparations in the management of asthma. There is therefore a need for carefully constructed trials of adequate power to assess some of these compounds further.

Conclusions

On the strength of the current evidence, few herbal preparations have been assessed adequately enough to draw conclusions on their efficacy and safety. Although some preparations have shown improvement in subjective measures of asthma symptoms, this is not strongly supported by changes in objective measures and may be compromised by poor study methodology. No clear recommendations for any herbal treatment of asthma can be made on the basis of this review.

Conflict of interest declarations

None known.

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Appendix 1: Characteristics of included studies.

Study	Participants & inclusion criteria	Intervention	Quality assessment (SG = sequence generation; AC = allocation concealment; B = blinding)	Study/ placebo sample sizes	Primary outcomes extracted	Secondary outcomes extracted	Results
Badria 2004 (Egypt)[18]	Hospital outpatients age 18-59 with clinical history and physical examination showing bronchial asthma. Smokers were excluded	Double-blind placebo-controlled trial (randomisation not described) of Boswellia carterii extract (500mg boswellic acid per capsule). two twice daily for 2 weeks.	SG= Unclear AC = Unclear B = Adequate	Three groups: mild (7/7) moderate (7/7) and severe(7/7)	Mean no. asthma attacks/week; mean no. night asthma attacks/week; mean FVC; mean FEV_1; mean PEF		Mean final FEV_1% predicted significantly higher on pooling the three subgroups (wmd: 7.24%; 95%CI 1.46 to 13.02)
Chan 2006 (Taiwan)[19]	Children aged 8-15 diagnosed asthmatic on GINA guidelines. Inclusion criteria included FEV_1 of >60% predicted and FEV_1 variability <30%.	Double-blind, placebo-controlled parallel group trial of 6 capsules of DCT (Din Chuan Tang) bd or placebo for 12 weeks	SG = Adequate AC = Unclear B = Adequate	28/24	PEFR, FEV_1, FVC,		No significant differences
Ebden 1989 (UK)[31]	Atopic mild, chronic asthma patients (4 male), mean age 33 (range 20-52). Smoking status not described.	Double-blind placebo controlled randomised, crossover trial of two Efamol capsules (Evening Primrose oil) 4 times daily for 8 weeks.	SG = Unclear AC = Unclear B = Adequate	12/12	PEFR		No significant differences
Gabrielian 2004 (Armenia)[20]	Subjects aged 25-65 years with bronchial asthma or chronic asthmatic bronchitis confirmed by a pulmonologist. Gender and smoking status not described.	Double-blind placebo controlled randomised trial of 2 capsules of 400 mg PulmoFlex per day for 3 weeks.	SG = Unclear AC = Unclear B = Adequate	21/9	FEV_1, VC, PEFR, frequency of asthma attacks, dyspnoea attacks, exercise tolerance	Patients experiencing deterioration, judged by examining doctor	patients experiencing a deterioration (RR 0.21; 95%CI 0.05 to 0.97, n=21)
Guinot 1987 (France)[32]	Atopic asthmatics (7 male) with FEV_1 >80% predicted & and positive skin prick test to house dust mite and no attacks in previous 2 months. Smoking status not stated.	Double-blind placebo-controlled randomised, crossover trial of BN52063 (ginkgolides A, B & C) 40mg capsules for 2x3 days with 7 day washout between	SG = Unclear AC = Unclear B = Adequate	8/8	FEV_1		No significant difference
Gupta 1979 (India)[21]	135 asthmatics attending chest clinic, male:female 2:25, age range 14-60. Smoking status not described.	Double-blind placebo controlled randomised trial. Placebo contains Ipecacuanha to mask side effect of nausea & vomiting. Treatment group given powder of 200mg tylohophora leaves and 160mg spinach leaves dried. Two packs of powder daily for 6 days	SG = Adequate AC = Unclear B = Adequate	71/64	FEV_1, PEFR, reduction in use of prescription medicines		No significant differences

Appendix 1: Characteristics of included studies continued.

Study	Participants & inclusion criteria	Intervention	Quality assessment (SG = sequence generation; AC = allocation concealment; B = blinding)	Study/ placebo sample sizes	Primary outcomes extracted	Secondary outcomes extracted	Results
Gupta 1998 (India)[22]	Subjects aged 18-75 (39 male) suffering from acute bronchial asthma presenting with breathlessness, wheezing, tachycardia, with or without cyanosis. Smoking status not described	Double-blind placebo-controlled trial (randomisation not described) of powdered gum resin of Boswellia serrata (S-Compound made by Rahul Pharma) 300mg boswellic acid capsules 3 times daily for 6 weeks	SG = Unclear AC = Unclear B = Adequate	40/40 Group taking treatment have more severe disease	Change in FEV_1, FVC and PEFR, number of asthma attacks during the treatment period.	Symptom scores	Significant increase in FEV_1 (400mL; 95%CI 230 to 570), PEFR (44.5 L/min; 95%CI 24.2 to 64.8) and FVC (400mL 95%CI 200 to 600)
Hederos 1996 (Sweden)[23]	60 children aged 1-16 yrs with atopic dermatitis. 22 patients (13 male 9 female) mean age 10.9 with asthma	Double-blind placebo-controlled randomised parallel group trial of capsules containing 500mg evening primrose oil (40 mg GLA). Children 1-12 years took 4 capsules twice daily. Children over 12 took 6 capsules twice daily for 16 weeks.	SG = Adequate AC = Unclear B = Adequate	12/10	PEFR, number of days with extra asthma medication.		Asthma sub-group not reported separately. Author was contacted but responded that results were not avallabie. Paper reported 'no clinical effect at all on PEFR or overall impression of asthma'
Hosseini 2001 (Iran)[33]	Patients referred to allergy clinic (12 female, 10 male) age 18-60 with baseline FEV_1 30-75% predicted. Smoking status unknown	Double-blind placebo-controlled randomised, crossover study of Pycnogenol 1mg/lb/day to a maximum of 200mg/day for four weeks, crossed over for a further four weeks.	SG = Unclear AC = Unclear B = Unclear	22/22	FEV_1; FEV_1/FVC ratio	Symptom scores graded 1 mild intermittent to 4 severe persistent	No significant differences
Hsieh 1996 (China)[13]	334 asthmatic children age 6-15, diagnosed by ATA criteria.with stable asthma, classified as: Group A - deficent in kidney energy, Group B spleen energy, and Group C both.	Double-blind placebo-controlled quasi-randomised (allocated according the order of visiting) trial of Specific herbal regimen for each group: Herb A = Liu-Wei-D-Huang-Wan; Herb B: Shen-Ling-Bia-Shu-San; Herb C: Jai-Wei-Si-Jun-Zi-Tang. 1 pack three times daily for 6 months.	SG = Inadequate AC = Unclear B = Adequate	Group A: 32/34 Group B: 74/64 Group C: 55/44	Change in early morning and evening PEFR	Symptom score graded 0 asymptomatic to 4 severe on 5 point scale	No significant differences in primary outcomes. Symptom scores improved for Liu-Wei-Di-Huang-Wan (WMD -0.40; 95%CI -0.66 to -0.14) and Shen-Ling-Bai-Shu-San (WMD -0.31; 95%CI -0.58 to -0.04)
Hsu 2005 (China)[24]	Children aged 5-18 years (actual age range 5 - 55 years; clarification not received). Inclusion criteria: FEV_1 >60% predicted; reversibility =>15%; 2 positive skin-prick tests, history of atopy.	Double-blind placebo-controlled randomised trial of Mai-Men-Dong-Tang given as 800mg or 400 mg in capsules twice daily for 17 weeks.	SG = Unclear AC = Inadequate B = Adequate	800mg bd:40 400mg bd:40 Placebo:20	FEV_1% predicted, non of subjects experiencing >5% improvement in FEV_1 after 4 months	Symptom scores grading cough wheeze and breathlessness each as 0 asymptomatic to 3 severe; total score 0 to 9 reported	Significantly more subjects on pooled analysis showed at least 5% increase in FEV_1 at the end of treatment (RR=8.00; 95%CI 2.02 to 31.71)

Appendix 1: Characteristics of included studies continued.

Study	Participants & inclusion criteria	Intervention	Quality assessment (SG = sequence generation; AC = allocation concealment; B = blinding)	Study/ placebo sample sizes	Primary outcomes extracted	Secondary outcomes extracted	Results
Juergens 2003 (Germany)[30]	Subjects meeting NHLBI criteria for asthma recruited from outpatient clinic age 32-75, 50% male. All taking 5-24mg oral prednisone daily. Smoking status not described	Double-blind placebo-controlled randomised trial of 1.8-cineol (eucalyptol: Soledum Capsules) 200mg three times daily for 12 weeks.	SG = Adequate AC = Adequate B = Adequate	16/16	Change from baseline oral steroid dosage, days stable on reduced dose, cumulative dose reductions, lung function with 2.5mg and 5mg reduction of prednisolone	Dyspnoea score Patient global assessment of efficacy Physician global assessment of efficacy. Assessed using "validated scales" which are not described.	Significant reduction in oral steroid dose (2.84mg; 95%CI 1.00 to 4.68) and significantly more patients tolerating 5mg reduction in steroids (RR=3.00 95%CI 1.23 to 7.34) Dyspnoea score (WMD -1.5; 95%CI -0.58 to -2.42) Patients', global assessments of efficacy (WMD-0.70; 95%CI -0.02 to - 1.38) Physicans' global assessments of efficacy (WMD-1.50; 95%CI -0.82 to -2.18)
Lau 2004 (USA)[14]	Children aged 6-18 yrs (35 male) with mild-moderate asthma recruited hospital. Inclusion criteria asthma symptoms defined by ATS criteria; FEV_1 50-85% predicted	Double-blind placebo-controlled randomised trial of Pycnogenol 1 mg/lb body weight in 2 divided doses daily for three months	SG = Unclear AC = Adequate B = Adequate	30/30	PEFR, use of oral medication	Symptom scores graded 0 asymptomatic to 4 severe	Significant increase in final PEFR% predicted (17.85% 95%CI 12.9 to 22.8) Symptom score SMD -3.84 (95%CI -2.97 to -4.72) Use of albuterol -2.1 puffs/24 hours (95%CI -1.67 to 0 -2.53)
Lee 2004 (UK – Scotland)[34]	Atopic asthmatic outpatients mean age 45 (7 female). Inclusion criteria: all sensitised to at least 2 aeroallergens including house dust mites and stable on inhaled orticosteroids for at least 3 months. Smoking status not described.	Double-blind placebo-controlled randomised crossover trial of Butterbur 25mg (Petaforce ®) twice daily	SG = Unclear AC = Unclear B = Adequate	16/16	FEV_1, PEFR, FEF25-75		No significant differences
Mansfeld 1998 (Germany – translated)[35]	Children from outpatient clinic /mean age 7.8 (15male). Inclusion criteria: Age 4-12 years with 10%FEV_1 change post-fenoterol.	Double-blind placebo-controlled randomised crossover trial of 35mg Ivy leaf extract one pill taken twice daily over two three-day periods with a washout of between 3 and 5 days	SG = Unclear AC = Unclear B = Unclear	Total 28, distribution not clear.	FEV_1, FVC, VC		No effect sizes could be estimated from the data
Mathew 1974 (India)[25]	Subjects were getting asthma symptoms daily or several times a week for the past few weeks and had a past history of symptoms of asthma. No information on gender, ages, or smoking status	Double-blind placebo-controlled randomised trial of alkaloids of Tylophora indica extracted from dried leaves, 0.5mg with 0.5mgm glucose, one packet taken daily for six days. With extended 12 week follow up.	SG = Adequate AC = Adequate B = Adequate	59/64	FEV_1, PEFR, amount of prescribed drugs used.	Symptom scores graded from 0 – no symptoms adding 1 for every ½ hour symptoms/day Total clinical improvement (calculated from scoring of rhionchi. Drug use and symptom score) at 1 and 12 weeks	Significantly more patients showed >15% increase in FEV_1 after 1 week (RR 2.19 95%CI 1.08 to 4.42), >20% increase in PEFR after 1 week (RR 2.87; 95%CI 1.71 to 4.81) and after 12 weeks (RR 2.37; 95%CI 1.05 to 5.31). Scores for drug consumption reduced after 1 week (RR 2.60; 95%CI 1.60 to 4.24) and 12 weeks (RR 2.29; 95%CI 1.13 to 4.66)

Appendix 1: Characteristics of included studies continued.

Study	Participants & inclusion criteria	Intervention	Quality assessment (SG = sequence generation; AC = allocation concealment; B = blinding)	Study/ placebo sample sizes	Primary outcomes extracted	Secondary outcomes extracted	Results
Murali 2006 (India)[26]	Volunteers with asthma age 15-50 recruited from hospital advertisement. Incusion criteria >15% improvement FEV_1 post bronchodilator. Smokers excluded.	Double-blind, placebo-controlled parallel group trial. Randomisation to 4 arms: 3 caps daily of Indian herbal preparation DCBT4567-Astha-15, salbutamol plus theophylline, salbutamol alone or placebo for 12 weeks.	SG = Adequate AC = Adequate B = Adequate	22/24	FEV_1 and a 15% improvement in FEV_1	Symptom scores grading dyspnoea, wheeze, cough, sleep disturbance from 0 absent to 3 severe.	No significant differences
Rouhi 2006 (Iran)[27]	Asthmatics receiving treatment for >12 months, age gender and smoking status not stated	Placebo controlled trial. 20 drops ginger solution 8hrly or placebo, probably one month run in &1 month treatment period, possibly 2 month treatment period	SG = Unclear AC = Unclear B = Unclear	46/46	Mean FEV_1, FVC, FEF25-75, use of "spray" (presume inhaler but not defined),	Presence or absence of dyspnoea, wheeze and chest tightness symptoms.	Dyspnoea (RR 0.84; 95%CI 0.72 to 0.98), Wheeze (RR 0.78; 95%CI 0.67 to 0.91) Chest tightness (RR 0.29; 95%CI 0.18 to 0.48)
Sekhar 2003 (India)[17]	60 in or outpatients with asthma, illness duration 6-24months. Ages & gender not stated. 50% smoked	Placebo-controlled trial of Devadaru Compound 3 tablets three times daily or liquid or placebo.	SG = Unclear AC = Unclear B = Unclear	20/20/20	PEFR		No effect sizes could be estimated from the data
Shivpuri 1969 (India)[36]	Subjects aged 10-45, gender and smoking not described. Diagnosis of asthma based on history of recurrent dyspnoea relieved by epinephrine or ephedrine with rhonchi during attack	Double-blind placebo-controlled randomised trial of chopped Tylophora indica leaves vs spinach leaves (placebo) cut into small pieces; one leaf daily for 6 days with follow up until the 12th week.	SG = Unclear AC = Adequate B = Adequate	53/57	Amount of prescribed drugs taken in 24 hours;	Total clinical improvement at 1 and 12 weeks (as used by Matthew 1974)	No effect sizes for primary outcome could be estimated from the data. Contributed to meta analysis of clinical improvement.
Shivpuri 1972 (India)[37]	Ages and smoking status not stated, 91 male Diagnosis as per Shivpuri 1969 above	Double-blind placebo-controlled randomised trial of dry alcholic extract of Tylophora leaves with 1g glucose powder for 6 days with follow up until the 12th week.	SG = Unclear AC = Adequate B = Adequate	103/92	Amount of prescribed drugs which had to be taken.	Total clinical improvement at 1 and 12 weeks (as used by Matthew 1974)	No effect sizes for primary outcome could be estimated from the data. Contributed to meta analysis of clinical improvement.
Tamaoki 1995 (Japan)[28]	Non-smokers with mild asthma aged 19-46 (12 males). Inclusion criteria: occasional symptoms controlled by β_2-agonists on demand, no exacerbation in previous 4 weeks.	Placebo-controlled, randomisation and double-blinding not described, trial of nebulized menthol 10 mg twice a day (manufactured by Hohei Co.) for 4 weeks.	SG = Unclear AC = Unclear B = Adequate	11/10	Vital capacity, FEV_1 and VC as % predicted, change in PEFR%, wheezing episodes/week,	Use of reliever inhalers (puffs/week) recorded in diary	No significant differences in primary outcome measures Reduction in use of reliever inhalers WMD -2.30 (95%CI -3.13 to -1.47)

Appendix 1: Characteristics of included studies continued.

Study	Participants & inclusion criteria	Intervention	Quality assessment (SG = sequence generation; AC = allocation concealment; B = blinding)	Study/ placebo sample sizes	Primary outcomes extracted	Secondary outcomes extracted	Results
Thiruvengadam 1978 (India)[38]	Gender ages and smoking status not reported. Inclusion criteria: history of asthma for at least 2 years with demonstrable reversal.	Double-blind placebo-controlled randomised crossover trial of capsules containing 350mg powdered Tylophora leaf daily for seven days, two-day washout, then the groups crossed over for another seven days	SG = Unclear AC = Unclear B = Adequate	8/7	VC PEFR, MBC (maximum breathing capacity), wheezing attacks, nocturnal dyspnoea, cough chest tightness		No effect sizes could be estimated from the data
Thomas 2006 (Scotland)[39]	Subjects aged 22-73, median daily dose beclomethasone 800mcg (range 0 - 4000). Smoking status not described	Double-blind placebo-controlled randomised crossover trial of AKL1, a herbal mixture including Gingko bilboa with 4 weeks baseline, 12 weeks treatment, 8 weeks washout and 12 weeks treatment period.	SG = Unclear AC = Unclear B = Adequate	32/32	FEV_1, PEFR	Asthma control questionnaire (ACQ). Leicester cough questionnaire	No significant differences in primary or secondary outcome measures comapred with placebo. Higher no of improved scores in ACQ in treatment group (RR 2.29; 95%CI 1.09 to 4.79)
Urata 2002 (Japan)[40]	Non smokers mean age 42 (15 male) with mild to moderate asthma on ATA criteria. Atopy confirmed with skin prick testing,	Double-blind placebo-controlled randomised crossover trial of 2.5g daily powdered TJ-96 -Saiboku-to then4 week washout, then crossover	SG = Unclear AC = Unclear B = Adequate	32/32	FEV_1, FVC	Symptom score graded 0 asymptomatic to 3, severe attacks on >4/days per week	Mean final FEV_1% predicted significantly higher: 86.9% vs 82.1%, difference 4.8%; 95%CI 1.67 to 7.93, $p<0.01$ Symptom score -0.90; (95%CI -0.74 to -1.06)
Ziboh 2004 (USA)[29]	Subjects age range 16-71 (63 male). Inclusion criteria: mild or moderate persistent asthma. Smoking status not described.	Double-blind placebo-controlled randomised trial of two capsules twice a day each containing Borage oil 500 mg GLA for twelve months.	SG = Unclear AC = Unclear B = Adequate	27/27	FEV_1		No effect sizes could be estimated from the data